# UTILIZATION PATTERN OF STATINS IN AN INDIAN POPULATION

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*In partial fulfillment for the requirement of the Degree of*

## MASTER OF PHARMACY

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**Submitted by**


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# CERTIFICATE

This is to certify that the dissertation work entitled **"UTILIZATION PATTERN OF STATINS IN AN INDIAN POPULATION"** submitted by **Mr**. **NIKHIL RAJ P.V** is a bonafide work carried out by the candidate under the guidance of **Dr. SUCHANDRA SEN, M.PHARM., Ph.D.** and submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy in Pharmacy Practice** at the Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore, during the academic year 2011-2012.

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# DECLARATION

I do hereby declare that the dissertation work entitled **"UTILIZATION PATTERN OF STATINS IN AN INDIAN POPULATION"** submitted to the Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy Practice,** was done by me under the guidance of **Dr. SUCHANDRA SEN, M.PHARM., Ph.D.** at the Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore, during the academic year 2011-2012.

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# EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"UTILIZATION PATTERN OF STATINS IN AN INDIAN POPULATION"** submitted by **Mr. NIKHIL RAJ P.V,** University **Register No: 26107285** to the Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmacy Practice** is a bonafide work carried out by the candidate at the Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore and was evaluated by us during the academic year 2011-2012.

**Examination Center:** KMCH College of Pharmacy, Coimbatore

**Date:**

**Internal Examiner** **External Examiner**

**Convener of Examination**

*DEDICATED*

*TO*

*GOD ALMIGHTY,*

*MY BELOVED PARENTS,*

*NEERAJ &*
*PRAJINA*

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# *Abbreviations*

# ABBREVIATIONS

| | | |
|---|---|---|
| ADR | : | Adverse drug reactions |
| ATP III | : | Adult Treatment Panel III |
| CHD | : | Coronary Heart Disease |
| CVD | : | Cardio Vascular Disease |
| HDL-c | : | High Density Lipoprotein Cholesterol |
| HMG-CoA | : | Hydroxy-3-methylglutaryl coenzyme A |
| LDL-c | : | Low Density Lipoprotein |
| NCEP | : | National Cholesterol Education Program |
| TC | : | Total Cholesterol |
| TG | : | Triglyceride |
| VLDL | : | Very low density Lipoprotein |

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# *Introduction*

# INTRODUCTION

Atheroma is a focal disease which affects the intima of large as well as medium sized arteries. Numerous risk factors for atheromatous disease were recognized by epidemiological studies. Some of them cannot be altered (e.g. family history of ischemic heart disease. Dyslipidemia is one of the contributing factors for the cardiovascular disease which can be modified and is a potential target for therapeutic drugs (**Rang and Dale, 2003**).

## LIPOPROTIEN TRANSPORT IN HUMAN BODY

Lipids and cholesterols are transferred in the blood as macromolecular complexes. These macromolecular complexes are called lipoproteins. The central cores of these complexes have a hydrophobic lipid in a hydrophilic coat which is polar in nature. The lipoproteins are classified into four groups based on the fraction of the core lipids and the type of apolipoprotiens. These four groups differ in their density and the size. (**Rang and Dale, 2003**)

The four types of lipoproteins are

- Low Density lipoprotein (LDL)
- High density lipoproteins(HDL)
- Very low density lipoproteins (VLDL)
- Chylomicrons

## DYSLIPIDIMIA

Dyslipidemia is defined as the presence of abnormal amount of lipids in the blood. The risk for cardiovascular disease increases with increased LDL cholesterol concentrations and decreased HDL cholesterol concentrations. (**Rang and Dale, 2003**)

Statins are used for primary and secondary prevention of cardiovascular diseases. When it is used to treat dyslipidemia in patients without any history of cardiovascular disease or atherosclerotic vascular disease it termed as primary prevention and when used in patients with a history of cardiovascular diseases or cardiovascular risk factors is said to be secondary prevention (**Chaiyakunapruk et al., 2010**).

All statins act by competitively inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, which is accountable for the change of HMG-CoA to mevalonate. This results in a compensatory increase in the number of LDL receptors, primarily in the liver, an increase in LDL plasma clearance and a reduction in LDL production. Although the most pronounced effect of statins is the lowering of LDL-C levels, these agents also increase HDL-C and decrease total cholesterol and plasma triglycerides (**Cheryl, 2007**).

Cardiovascular diseases are progressively rising as the major cause of death throughout the world. The implications of cardiovascular diseases are more significant in India. About 3.75 million deaths were reported, due to cardiovascular diseases in 2010, across India. Out of this 2 million deaths were due to coronary artery diseases and heart attacks. The Lancet finds that in the next two years India will put up with 60% of the world's heart disease burden, additionally studies revealed that the average age of patients prone to heart disease is lower among Indian population than in the developed countries but are more likely to have various heart diseases (**Kanniyappan et al., 2010**).

National Commission on Macroeconomics and Health (NCMH), a government of India undertaking estimates that there will be around 62 million patients with CAD by 2015 in India. Out of this 23 million patients are expected to be at the age less than 40 years. The main cause of CAD is atherosclerosis of large and medium sized arteries and dyslipidemia is considered as the primary cause (**Sawanth et al., 2008**).

More than 40% of individuals over 65 years of age seek medical treatment and are hospitalized for coronary diseases at least once in their lifetime. The quality of life of the patients will be adversely affected by the recurrent hospitalization and disability in these patients. The estimated prevalence of coronary artery disease in these patients are more than 40% and is associated with high risk of mortality ( **Parikh et al.,2010**).

Although the treatment of dyslipidemia for the prevention of cardiovascular diseases is common, all the patients who are treated with statins do not get the benefits. Noncompliance and discontinuation of the therapy results in failure of the treatment. The risk of non compliance of the statin therapy varies from 15%-30% within the first year when the therapy is initiated (**Caspard et al., 2005**).

Rhabdomyolysis is the major ADR caused by statins, but the incidence is very rare since it is well tolerated in patients. The incidence of rhabdomyolysis apart from the use of statins is only 50%. Diffuse myalgias and weakness over several days will present in case of statin induced rhabdomyolysis, the presentation of the symptoms however varies in patients. The symptoms of rhabdomyolysis may be atypical so strict monitoring of the patients is needed especially in patients having elevated creatine kinase level. Patients with rhabdomyolysis show symptoms like common muscle pain and fatigue. The average time for developing statin induced rhabdomyolysis is approximately 1 year (**Antons et al., 2006**).

Statins are highly effective for the secondary prevention of CAD and are well tolerated in patients. Hence they are the mainstay for CAD patients. Drug utilization evaluation studies are important factors related to prescribing, dispensing, administering and usage of medication, and its associated events. The study is also aimed to note the adverse drug reactions reported and to relate them to the different characteristics of the study population. From the information on adverse drug reactions, changes can be made and drug use improved. This can prevent unnecessary withdrawal of the medication by the patient himself.

There is not much information available regarding the utilization pattern of statins in the Asian population, hence the study was undertaken to determine the utilization pattern of statin in an Indian clinical setting.

# Review of Literature

# REVIEW OF LITERATURE

Hyperlipidemia is a major cause of increased atherogenic risk. Genetic disorders and diets enriched in saturated fat and cholesterol contribute to the elevated lipid levels. After recognizing hypercholesterolemia as the major risk factor, numerous drugs have been developed to reduce the cholesterol levels. The drugs were used in well controlled studies of patients with high cholesterol levels caused primarily by the increased level of low density lipoproteins. The result of these trials indicated that mortality due to coronary heart disease is reduced by 30% to 40% and the non fatal events are also found to be reduced significantly. (**Gillman, 2006**)

The HDL cholesterol was also recognized as predictor cardiovascular events across the TNT study cohort when the HDL cholesterol and the LDL-C were taken as a continuous variable and subjects were stratified in proportion to the level of HDL cholesterol. When the analysis was done according to LDL cholesterol level in patients on treatment with statins, the association between HDL cholesterol level and major cardiovascular events was found at borderline significance. There was a high level of significance between the increased HDL level and reduced cardiovascular events during the analysis. (**Barter et al., 2007**)

## DYSLIPIDEMIA

Dyslipidemia is characterized by three lipid abnormalities: elevated triglycerides, elevated LDL particles, and reduced HDL cholesterol. Often the lipoprotein concentrations in this lipid triad are not categorically abnormal, but are only marginally deranged. More sophisticated methodology than that used in routine clinical practice can identify these multiple interrelated abnormalities. Still, in some persons, low HDL-cholesterol levels can occur in the absence of other lipoprotein abnormalities. These persons are said to have

isolated low HDL. They are not common in the general population, however; more often, low HDL cholesterol occurs as a component of the lipid triad. Because of the common occurrence of the lipid triad, the relation of the lipid triad as a whole to CHD risk will be considered, and whether the entire triad is a target for therapy. (**NCEP ATP III**)

**Table 1: ATP III Classification of LDL, TOTAL and HDL Cholesterol.**

| **LDL CHOLESTEROL** | |
|---|---|
| <100 | Optimal |
| 100-129 | Near optimal/ above optimal |
| 130-159 | Borderline high |
| 160-189 | High |
| ≥190 | Very high |
| **TOTAL CHOLESTEROL** | |
| <200 | Desirable |
| 200-239 | Borderline high |
| ≥240 | High |
| **HDL CHOLESTEROL** | |
| <40 | Low |
| ≥60 | High |

## EPIDEMOLOGY

Cardiovascular disease is considered as the major cause of death in older individuals, and it was estimated that over 80% of deaths among these patients are due to coronary heart disease or stroke. The most important adaptable risk factor recognized for cardiovascular disease is hyperlipidemia. Recent guidelines propose the use of statins to reduce LDL-C to the targets based on risk factors of the individuals and it was stated that age of the patients should not be a barrier to the therapy for treating dyslipidemia. (**Wenger et al., 2010**)

In a study conducted from January 2006 to 31$^{st}$ December 2006, in 1805 subjects at an age group ≥ 40 years, health condition of the patients were assessed by physical checkups and laboratory profiles like complete fasting lipid profiles and blood glucose levels. The data were analyzed according to National Cholesterol Education Program Adult Treatment Panel (ATP) III guidelines and American Diabetes Association (ADA). The incidence of dyslipidemia was higher in men than in women. Among all patients who had a total cholesterol concentration ≥ 200mg/dl, around 39% were males and 24.0% were female patients. High density lipoprotein cholesterol (HDL-C) was unusually low in about 64.0% males and about 34.0% in females. The incidence of dyslipidemia is found to be high in the age group of 31-40 years. (**Sawant et al., 2008**)

Cardiovascular disease is estimated to be the principal cause of mortality throughout the world. In a study carried out in Framinghamin the year 1949 it was monitored that among the 5000 residents living in Framingham, Massachussetts, U.S.A, cigarette smoking, diabetes mellitus, hypertension, and increased cholesterol levels are the changeable risk factors for atherosclerosis, especially coronary heart disease and the age is was found to be a factor which is non modifiable. The risk for cardiovascular diseases is found to be more in males than females. (**Winkelmann et al.,**)

The involvement of high cholesterol levels in causing coronary heart disease and other vascular events has been in the disputed until about a decade ago. The coming out of HMG-CoA reductase inhibitors or statins as potent lipid lowering drugs put an end to this debate. In various large randomized clinical trials it was revealed beyond doubt, that LDL cholesterol reduction from the baseline in patients with dyslipidemia will significantly reduce cardiovascular morbidity and mortality. (**Winkelmann et al.,**)

Dyslipidemia is identified as the major risk factor for the coronary diseases at an early stage in the lifespan. A study was conducted in Warangal district of Andhra Pradesh which included 1496 adults and older individuals. Health status was assessed by questionnaires and physical findings. Out of the total patients diagnosed with dyslipidemia 52.7% were males and 42.9% were females. HDL-C was unusually low in 7% of males and in 1.6% of females. The incidence of hypercholesterolemia, hypertriglyceridemia and abnormally low HDL cholesterol were predominant in all age groups, But in middle age group (40– 59 years) this increase was found to be highly significant. The prevalence of dyslipidemia has increased considerably in the last 10 years in metropolitan adult populations in Warangal district, Andhra Pradesh. (**Estari et al., 2009**)

The frequency of cardiovascular events increases sharply with the increase in age. The incidence of CV disease and associated risk factors are considerably higher in older individuals. Cardiovascular disease is the most important reason for death in older patients, out of this over 80% of deaths are reported due to coronary heart disease (CHD) or stroke occur in individuals 65 years of age or older. So the prevention and recurrent of CV events in older individuals remains a major concern. (**Wenger et al., 2010**)

Cardiovascular disease (CVD) includes a wide verity of diseases like ischemic heart disease, coronary heart disease, cerebrovascular disease like stroke, rheumatic heart disease

and heart failure.17 million deaths ie, 30% of total deaths were reported due to CVD by WHO in 2008 Of these, 7.6 million are due to heart attacks. The incidence of CVD is found to be highly prevalent in low income countries. (**Kanniyappan et al.,2010**)

**TREATMENT OF DYSLIPIDEMIA**

**Table 2: The target of the therapy (Adapted from NCEP ATP III Guidelines)**

| RISK CATEGORY | LDL GOAL | LDL LEVEL AT WHICH TO INITIATE THERAPEUTIC LIFESTYLE CHANGES | LDL LEVEL AT WHICH TO CONSIDER DRUG THERAPY |
|---|---|---|---|
| CHD or CHD Risk equivalents (10 year risk >20%) | <100mg/dL | ≥100mg/dL | ≥ 130 mg/dL (100-129 mg/dL: drug optional)* |
| 2+risk factors (10 year risk ≤20%) | 130mg/dL | 130mg/dL | 10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL |
| 0-1 Risk Factor | <160 mg/dL | ≥160 mg/dL | ≥190 mg/dL160-189mg/dL: LDL-lowering drug optional) |

The Third Expert Panel Report of the National Cholesterol Education Program (NCEP) 2 recognizes that LDL-Cholesterol should be the primary target for the management of hyperlipidemia. The incidence of cardiovascular events is significantly reduced by dropping LDL cholesterol levels. So the recommendations focus mainly upon LDL-Cholesterol reduction as the primary target. A number of primary and secondary clinical trials demonstrated that statins can reduce the incidence of coronary events and its recurrence. (**Cheryl, 2007**).

Statin therapy is recommend by the current guidelines to decrease LDL Cholesterol to target level and LDL target is based on the patients cardiovascular risk score. The pharmacokinetic profiles of statins vary with age of the individual. But the variations are not clinically relevant. Usually dose adjustments based on age are not advocated in the clinical settings. The lipid-lowering therapy using statins remains widely underutilized in middle age. There is more clinical inertia associated with statins use in older patients. This occurs despite extensive evidence of CV risk reduction associated with the use of statin in this age group. (**Wenger et al., 2010)**

The prevalence of cardiovascular disease in hospitalized patients is very high. This will cause a significant clinical and economic burden. Statins are highly effective in reducing mortality and recurrent hospitalization in older patients with CAD. (**Winkelmann et al.,**)

There are many factors which contribute to CVD. Lifestyle changes are considered as the main part any treatment strategy. Pharmacotherapy will be needed in those patients who cannot achieve the risk reduction by lifestyle changes and for patients who are at high risk. The primary aim of the pharmacotherapy is to reduce the lipid level of the patients with or without the history of CVD. (**Kanniyappan et al.,2010**)

## STATINS

Statins were isolated from a mold, *Penicillium citrinum,* and identified as inhibitors of cholesterol biosynthesis in 1976 by Endo and colleagues. Subsequent studies by Brown and Goldstein established that statins act by inhibiting HMG-CoA reductase. The first statin studied in humans was Compactin, renamed Mevastatin, which demonstrated the therapeutic potential of this class of drugs. However, Alberts and colleagues at Merck developed the first statin approved for use in humans, lovastatin (formerly known as Mevinolin), which was

isolated from *Aspergillus terreus*. Five other statins are also available, pravastatin and Simvastatin are chemically modified derivatives of lovastatin. atorvastatin, fluvastatin, and rosuvastatin are structurally distinct synthetic compounds. (**Gillman, 2006**).

The statins are the most effective and best-tolerated agents for treating dyslipidemia. These drugs are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, which catalyzes an early, rate-limiting step in cholesterol biosynthesis. Higher doses of the more potent statins (Atorvastatin and simvastatin) also can reduce triglyceride levels caused by elevated VLDL levels. (**Gillman, 2006**)

Multiple well-controlled clinical trials have documented the efficacy and safety of simvastatin, pravastatin, lovastatin, and atorvastatin in reducing fatal and nonfatal CHD events, strokes, and total mortality. Rates of adverse events in statin trials were the same in the placebo groups and in the groups receiving the drug. This was true with regard to noncardiac illness and the two laboratory tests, hepatic transaminases and creatine kinase (CK) that are commonly monitored in patients taking statins. (**Gillman, 2006**)

A number of drugs are presently accessible for the management of dyslipidemia, but the most effective agents recognized are HMG CoA reductase inhibitors or statins. The main agents in this category are includes atorvastatin, simvastatin, rosuvastatin, fluvastatin, lovastatin and pravastatin. All agents were found effective in lowering low-density lipoproteins, total cholesterol and triglycerides and they are capable of increasing high-density lipoproteins also. LDL cholesterol was reduced by these agents in a in a dose dependent way, about 20-38% with primary doses and 35-61% with the height dose. Rosuvastatin the newest among all the statins has been named as “superstatin” since it has the capability to decrease LDC-C and increase HDL cholesterol to a bigger extent than the other

accepted class of statins. Rosuvastatin can reduce LDL-C by 63% at of 40 mg dose. The most effective class of statin in reducing the triglyceride level is atorvastatin. (**Cheryl, 2007**).

Statins are used for primary and secondary prevention of cardiovascular diseases. When it is used to treat dyslipidemia in patients without any history of cardiovascular disease or atherosclerotic vascular disease it termed as primary prevention and when used in patients with a history of CVD or CVD risk factors is said to be secondary prevention .LDL level less than 100mg/dl for patients with cardiac diseases or cardiac risk factors and less than 70mg/dl is suggest by recent guidelines for patients with high risk. (**Chaiyakunapruk et al., 2010**)

Statin therapy holds great promise for dropping the frequency of major vascular events, surgical procedures, and stroke in patients at high risk. Statins established safety in a greater part of the patients using them. Side effects observed in clinical trials are very less and there was only a limited report in post-marketing surveillance when compared to the very large population safely on treatment with statins. Statins are not completely free of side effects and it should be used properly and with care. If statins are used with close monitoring in patients with high risk for developing ADR the chances of developing clinically important myopathy can be significantly reduced. (**Pasternak et al., 2002**)

An open-label, randomized, multicenter trial was carried out for 6-weeks in 2,431 adults with an aim to compare the lipid reduction properties of different class of statins like rosuvastatin with atorvastatin, pravastatin, and simvastatin at various doses. Secondary aim of the study was to compare Rosuvastatin with comparators for additional properties of lipid alterations and accomplishment of NCEP ATP III and Joint European Task Force LDL cholesterol goals. The study revealed that the average LDL-C reduction by rosuvastatin is 8.2% greater than atorvastatin, 26% more than pravastatin, and 12% to 18% more than simvastatin. Treatment goal according to NCEP ATP III guidelines was achieved by 82% to

89% of patients receiving rosuvastatin at doses 10 to 40 mg relative to 69% to 85% of patients treated with atorvastatin 10 to 80 mg. (**Jones et al., 2003**)

Statins are metabolized by the cytochrome P450 3A4 enzyme systems so they will interact with drugs using the same pathway. The common drugs which can interact with statins include macrolides, calcium channel blockers, azole antifungal, and nefazodone resulting in elevated concentration of statin in blood and myositis. Lovastatin and simvastin have more chances for this interaction. Other statins are not much depending on this enzyme and the chance for this type of interaction is very less Eg. Pravastatin which is not metabolized by this enzyme system (**Cheryl et al., 2007**)

Age was found to be a major risk factor for CVD in older patients, independent of other cardiovascular risk factors since the older individuals remains undertreated with statins. In older patients even they are prescribed with lipid lowering agents LDL-C targets are not accomplished usually. There are so many evidences that support the positive outcomes of statin therapy in geriatric population. In spite of the broad evidences that demonstrated clear benefits with statin therapy in older individuals, the geriatric population remains undertreated. Short of awareness of clinical benefits and issues regarding the safety of statins in geriatric population may account for the failure to provide appropriate treatment. However, if these population is treated according to the current guidelines and achieving their target LDL-C goals, the incidence of cardiovascular events will be significantly reduced in this high-risk population. Older patients are expected to get benefited by evidence based approach in terms of overall cardiovascular burden. (**Wenger et al., 2010**)

About fourteen clinical trials were conducted in 34,272 participants, out of which in 11trials take on patients with specific conditions like raised lipids, diabetes, hypertension it was found that mortality was decreased by the use of statins where the endpoint was both

fatal and non fatal CVD. There was a significant reduction in coronary revascularization rates as well. The data regarding the harms of statin therapy in quality of life of the patients is not well established. Reductions in mortality and factors which affects the quality of life of the patients like main vascular procedures and revascularization were observed in some clinical trials. There was no muscle pain and associated adverse drug reactions were not detected on treatment with statins. There were only a few evidences which states that primary prevention with statins may be cost effective and improve patient quality of life. Care should be taken while prescribing statins for primary prevention among patients with at low cardiovascular risk. (**Taylor et al., 2011)**

Data regarding the safety and effectiveness of the statins in the common clinical settings are not well known as the drug is widely utilized various patient groups outside the controlled clinical trial environment. Particularly geriatric patients with co morbidities and complex drug regimens, cognitive and functional impairment are often excluded from RCTs; so there will be limitations in the generalizability of RCTs to these populations. Therefore, the impact of statins on mortality and health service utilization in the clinical setting should be explored. (**Cooke et al., 2009**)

In a study conducted in a health maintenance organization setting it was found that persons aged below 50 years were at high risk of poor adherence to statin therapy and the assessment proposed that the relationship between age and gender may be reasonably steady after three years of therapy with statins. (C**aspard et al., 2005**)

**MECHANISM OF ACTION OF STATINS**

Statins exert their effects of LDL levels through a mevalonic acid-like moiety that competitively inhibits HMG-CoA reductase. By reducing the conversion of HMG-CoA to mevalonate, statins inhibit an early and rate-limiting step in cholesterol biosynthesis.

Statins affect blood cholesterol levels by inhibiting hepatic cholesterol synthesis, which results in increased expression of the LDL receptor gene. In response to the reduced free cholesterol content within hepatocytes, membrane-bound sterol regulatory enzyme binding proteins are cleaved by a protease and translocated to the nucleus. The transcription factors then bind the sterol-responsive element of the LDL receptor gene, enhancing transcription and increasing the synthesis of LDL receptors (**Horton et al., 2002**). Degradation of LDL receptors also is reduced. The greater number of LDL receptors on the surface of hepatocytes results in increased removal of LDL from the blood, thereby lowering LDL cholesterol levels. Some studies suggest that statins also can reduce LDL levels by enhancing the removal of LDL precursors (VLDL and IDL) and by decreasing hepatic VLDL production (**Salinas et al., 1998**). Since VLDL remnants and IDL are enriched in apoE, a statin-induced increase in the number of LDL receptors, which recognize both apoB-100 and apoE, enhances the clearance of these LDL precursors. The reduction in hepatic VLDL production induced by statins is thought to be mediated by reduced synthesis of cholesterol, a required component of VLDL (**Thompson, 1996**). These mechanism also likely accounts for the triglyceride-lowering effect of statins (**Ginsberg, 1998**) and may account for the reduction (~25%) of LDL-C levels in patients with homozygous familial hypercholesterolemia treated with 80 mg of atorvastatin or simvastatin.

## TRIGLYCERIDE REDUCTION BY STATINS

Triglyceride levels >250 mg/dl are reduced substantially by statins, and the percent reduction achieved is similar to the percent reduction in LDL-C (**Stein et al., 1998**). Accordingly, hypertriglyceridemic patients taking the highest doses of the most potent statins (simvastatin and atorvastatin, 80 mg/day; rosuvastatin, 40 mg/day) experience a 35% to 45% reduction in LDL-C and a similar reduction in fasting triglyceride levels (**Bakker-Arkema et**

**al., 1996; Ose et al., 2000; Hunninghake et al., 2004**). If baseline triglyceride levels are below 250 mg/dl, reductions in triglycerides do not exceed 25% irrespective of the dose or statin used (**Stein et al., 1998**). Similar reductions (35% to 45%) in triglycerides can be accomplished with doses of fibrates or niacin, although these drugs do not reduce LDL-C to the same extent as atorvastatin or simvastatin at the 80-mg dose.

## EFFECT OF STATINS ON HDL CHOLESTEROL LEVELS

Most studies of patients treated with statins have systematically excluded patients with low HDL-C levels. In studies of patients with elevated LDL cholesterol levels and gender-appropriate HDL levels (40 to 50 mg/dl for men; 50 to 60 mg/dl for women), an increase in HDL cholesterol of 5% to 10% was observed, irrespective of the dose or statin employed. However, in patients with reduced HDL levels (<35 mg/dl), statins may differ in their effects on HDL levels. Simvastatin, at its highest dose of 80 mg, increases HDL-C and apoA-I levels more than a comparable dose of atorvastatin (**Crouse et al., 2000**). In preliminary studies of patients with hypertriglyceridemia and low HDL-C, rosuvastatin appears to raise HDL-C levels by as much as 15% to 20% (**Hunninghake et al., 2004**). More studies are needed to ascertain whether the effects of statins on HDL-C in patients with low HDL-C levels are clinically significant.

## EFFECTS OF STATINS ON LDL CHOLESTEROL LEVELS

Statins lower LDL cholesterol by 20% to 55%, depending on the dose and statin used. In large trials comparing the effects of the various statins, equivalent doses appear to be 5 mg of simvastatin = ~15 mg of lovastatin = ~15 mg of pravastatin = ~40 mg of fluvastatin ; 20 mg of simvastatin = ~10 mg of atorvastatin and 20 mg of atorvastatin = 10 mg of rosuvastatin (**Jones *et al.*, 2003**). Analysis of dose-response relationships for all statins demonstrates that the efficacy of LDL lowering is log-linear; LDL is reduced by ~6% (from

baseline) with each doubling of the dose (**Pedersen and Tobert, 1996; Jones et al., 1998**). Maximal effects on plasma cholesterol levels are achieved within 7 to 10 days.

Statins are highly effective in reducing the cholesterol biosynthesis which occurs in liver. In the liver these lipids will be dispersed selectively and statin will organize the tone of lipid metabolism as well, by reducing the enzyme HMG-CoA reductase. Statins are well known for their capacity to reduce the LDL cholesterol which is positively correlated to its antithrombotic property. In addition to the hypolipidemic action they have antiatherosclerotic effects also. Since statins act by reducing the enzyme HMG-CoA reductase they have a positive pleotropic effect by modulating the mevalonate metabolism which can produce a sequence of critical molecules like isoprenoids for different cellular functions like cell growth and differentiation. As a result, statins decrease appreciably the frequency of coronary events and they are considered as the most efficient hypolipidemic agents for primary and secondary prevention of cardiovascular events. (**Stancu and Sima, 2001**)

**ADVERSE DRUG REACTIONS OF STATINS**

The adverse effects of statins are rare and usually mild which include headache, and GI symptoms (dyspepsia, flatus, constipation, and abdominal pain) and myalgias without CPK changes, Elevation in transaminase level is observed in 1-2%patients after 3-12 months of initiation of therapy (**Cheryl, 2007**)

The most common adverse drug reactions are muscle and liver toxicity. Usually statins are well tolerated in patients. The chances of myopathy are more in patients using drugs which inhibit the metabolizing enzyme cytochrome P450. The amount of statin in the blood was found to be elevated in such patients. The major inhibitors of the enzyme cytochrome P450 are the azole antifungals , fibrates and niacin. ( **Stancu and Sima,2001**)

Rhabdomyolysis is the major ADR caused by statins, but the incidence is very rare since it is well tolerated in patients. The incidence of rhabdomyolysis apart from the use of statins is only 50%. Diffuse myalgias and weakness over several days will present in case of statin induced rhabdomyolysis, the presentation of the symptoms varies in patients. Subacute progression of low back and proximal muscle pain may be present over weeks. Flu-like syndrome was observed in preclinical studies of rosuvastatin. (**Antons et al., 2006**)

The symptoms of rhabdomyolysis may be atypical so strict monitoring of the patients is needed patients having elevated creatin kinase level. Patients with rhabdomyolysis show symptoms like common muscle pain and fatigue. The average time for developing statin induced rhabdomyolysis is approximately 1 year. (**Antons et al., 2006**)

The evidence behind the finding of perioperative stage as a threat for statin-induced rhabdomyolysis is partial. In some case reports it was found that patients have rhabdomyolysis even after undergoing simple surgical procedures, but least number of patients reported muscle pain and muscle toxicity symptoms before hospital admission as well. The conditions of the patients on review proposed that there was a considerable profit to statin use in perioperative condition to coronary bypass or vascular surgery. In some other studies it was found that there was no harm and benefits in using statins in perioperative conditions. As a result of these contradictory results, the present strategy proposed that statins can be used in remission perioperatively and require close monitoring, and thereafter the therapy should be continued to get the advantages of reduced vascular events from beginning to end of the perioperative stage for all vascular procedures like coronary bypass. The therapy should be discontinued for all the patients with symptoms of muscle toxicity and in patients with extended tissue stress and postoperative calorie depletion. (**Antons et al., 2006**)

The main reason for the patients who remain undertreated with statin therapy is the fear of muscle toxicity. New approaches are recommended to manage statin induced rhabdomyolysis and for the treatment of dyslipidemia thereafter. In the common clinical practice the chances for statin induced rhabdomyolysis is very high because in controlled clinical trials the high risk populations, like geriatrics, were excluded. There are other risk factors like renal dysfunction, hepatic failure, and thyroid gland impairment. Recent investigations reveal that age, race, work outs, and perioperative conditions may contribute to statin induced muscle toxicity. The relationship between the risk of statin induced rhabdomyolysis and the drug level in the serum was explained in brief by pharmacokinetic theory and is found that conditions like metabolic syndrome can also contribute to rhabdomyolysis. (**Antons et al., 2006**)

Statins are the group of drugs which are prescribed for most of the patients with dyslipidemia. Statins have a numerous pleiotropic actions also. The antioxidant and anti-inflammatory properties of statins are well known and as a result they can control the process of angiogenesis and modulate the inflammatory process. Investigational facts advocate that statins are advantageous in heart failure because of their property to inhibit myocardial hypertrophy, and to reduce cardiomyocyte loss by controlling the process of apoptosis and it can also decrease oxidative stress and reinstate neurohormonal imbalance. Large prospective randomized controlled trials are needed to verify the beneficial effect of statins on cardiovascular outcome in heart failure patients and further elucidate the contributing mechanisms. Finally the statin dose and the interaction with co-administered drugs need to be studied. (**Tousoulis et al., 2007**)

The properties of statins to protect the renal damage in human beings are unknown. In a retrospective cohort study carried out in Canada with 213, 347 older patients, it was found

that in patients who underwent main surgical procedure around 2% had acute kidney damage. The mortality rate within 30 days in these patients was found to be around 3%. Before surgical treatment, 32% of patients were on treatment with statin. After statistical modification it was concluded that statins can preserve the kidney from acute injuries and lower the incidence of mortality in perioperative stage during an elective surgical procedure. (**Molnar et al., 2011**)

The patients prescribed with statins for dyslipidemia were at younger age group when compared to the non users of statins and males are more in this category and they had co morbid conditions like hypertension, diabetes mellitus and vascular diseases. The patients on statin therapy spent only a few days in hospital. But the prevalence of chronic kidney illness was found to be equal in both statin users and non users. (**Molnaret et al., 2011**)

Fatal events are reported in less than one million prescriptions which can be avoided by stopping the drug early in case of any adverse drug reactions. Cerivastatin is a class of statin which was withdrawn from the market in 2001 because it was having 10-50 fold more rate of causing fatal rhabdomyolysis. The mechanism behind myopathy is seems to be associated with elevated plasma levels of the drug and reduction of mevalonate-dependent metabolites.. Interaction with other drugs metabolised by the enzyme cytochrome P450 enzyme can increase the concentration of statins in plasma. (**Winkelmann et al., 2010)**

A study was conducted in Thailand in which 2479 patients with dyslipidemia were included. All the patients were first time users of statins and almost 90% of the subjects included in the study were prescribed with simvastatin. Atorvastatin and pravastatin were used by only 8% and 2% patients respectively. It was found that about 58% of the patients were on statin therapy for primary prevention. The study found out that in 80% of the patients using atorvastatin for secondary prevention is not actually needed by them because the target

was found to be achievable by using simvastatin. Only around 8% of the patients using simvastatin were not able to achieve their target LDL-C level. (**Chaiyakunapruk et al., 2011**)

The use of statins has considerably increased from 1.2% to 31.8% in the last 11 years. It was estimated that patients before cardiac hospitalization and who receive cardiac medications are the predictors of statin use. Older patients hospitalized for acute coronary syndrome with or without any cardiovascular intervention were less likely to be prescribed with a statin. Patients on antiplatelet therapy and on treatment with ACE inhibitors were less likely to be on treatment with statins after discharge from the hospital. There was no association between factors like renal disease, prior stroke, diabetes, hypertension with utilization of statins. (**Parikh et al., 2010**)

In a study conducted in 4232 older patients who were discharged from the hospital, about 40% of the patients were prescribed with statins on discharge. In multivariate models after modification for demographic and clinical characters, statins were found to produce a reduction of about 26% in the mortality and subsequent reductions in health service utilization, like re-hospitalizations, physician visits and coronary revascularization procedures. (**Cooke et al., 2009**)

A multicenter cohort study named The Multi-Ethnic Study of Atherosclerosis (MESA) was conducted in 6814 persons at an age group of 45 to 84 years without any cardiovascular problems in the year 2000 to 2002. The complete lipid profiles were attained in 6704 patients and evaluated for CVD risk and they were advised to report the use of lipid-lowering therapy. The drugs were prescribed according to the NCEP ATP III guidelines. Models were established to adjust the variables by using Poisson regression. 30% of the patients were diagnosed with dyslipidemia, 54.0% patients reported the use of statin therapy

and the target was achieved in 75.2% of patients. Men are more likely to be treated with drug therapy for dyslipidemia. The study concluded that dyslipidemia is familiar among patients without CVD and further investigations and programs to improve the quality of life of the patients are needed in future. **(Goff et al., 2006).**

# *Methodology*

# METHODOLOGY

## Objective

To evaluate the safety and efficacy of statins in an Indian population attending a cardiology clinic and thereby assess the utilization pattern of the drugs.

## Study design

It is a prospective study.

## Study setting

The study was conducted in Department of Cardiology, Kovai Medical Center and Hospital in Coimbatore, Tamil Nadu

## Study period

The study was conducted over a period of 6 months from July 2011 to December 2011

## Inclusion criteria

All patients diagnosed with dyslipidemia and cardiovascular risk factors, prescribed with statins for the first time in the Department of Cardiology, Kovai Medical Center Hospital Coimbatore.

## Exclusion criteria

a) Patients who were previously on Statin therapy will be excluded from the study.

b) Patients without a lipid profile at their first review.

**Source of data**

The data was collected from various sources such as patient's case reports, treatment charts and also through telephonic conversations with the patients.

**Study protocol**

Patients who met the study criteria were identified. The study was explained to the patients and their oral consent was taken. Ethical committee approval was obtained from Kovai Medical Center and hospital. Parameters like age, sex, current medications, past medical and medical history were collected from treatment charts and patient's case reports. Patient's adherence to statins was checked by using Morisky's 8 questionnaire through telephonic interview with the patients. Naranjo's causality assessment scale was used to assess the reported ADRs.

**Statistical Analysis**

Individual variables have been expressed as percentages or mean ± SE. The reduction LDL-C level from the baseline at review was compared using paired student't' test. p value of $\leq 0.05$ was taken as significant.

# Results

# RESULTS

In this prospective study, the utilization pattern of statins was evaluated in a total of 32 patients who were diagnosed with dyslipidemia for the first time and obtained their lipid profiles at least once during the study period. The LDL-C level of the patients was assessed at baseline and at review.

In the study population the prevalence of dyslipidemia was high in males than in females. 93.75% of the patients were males and the remaining 6.25% of the patients were females. (Table 3, Figure1). The age wise distribution of the patients using statins was given in Table 4, Figure 2. Most of the patients were at an age group of 61-70years.

In the study population 78.12% of the patients were using atorvastatin and 21.88% of the patients were using rosuvastatin. (Table 5, Figure 3). Among all the classes of statin atorvastatin 40mg was prescribed in most of the patients (28.12%). No patients were using atorvastatin 20mg and rosuvastatin 5mg. (Table 6, Figure 4).

Atorvastatin 80mg was found to produce maximum lipid reduction among all the other classes of statins in the study population (37.62%) and the least by atorvastatin 40mg (17.83%). Atorvastatin showed a mean lipid reduction of 21.29%,24.16% at doses of 5mg and 10mg respectively. Rosuvastatin 10mg showed 32.574% LDL-C reduction at review. (Table 7, Figure 5).

Statin use were assessed in terms of type of prevention and found that 59.37% of patients were prescribed for secondary prevention and the remaining 40.62% of patients were on treatment with statins for primary prevention of cardiovascular diseases. (Table 8, Figure 6). Patient's adherence to statin therapy was checked by using Morisky's 8 questionnaire. 67.4 % of patients were highly adherent to their treatment plan. 22.58% of patients showed

medium adherence and 9.67% of patients showed low adherence to their treatment plans. (Table 9, Figure 7).

Statins are well tolerated in most of the patients. Muscle pain was the only Adverse Drug Reaction found in the study population. It was noted that 74.2% of the patients were free from muscle pain and 25.8% patients complained of muscle pain. (Table 10, Figure 8).

The adverse drug reactions and patient's age were related in the study population and understood that 87.5% of the patients who developed muscle pain were at an age group of 61-70 years and 12.5% of patients were at an age group of 21-30 years.(Table 11, Figure 9).The prevalence of ADR was found to be more in geriatric population.

The mean age of the patients using atorvastatin and rosuvastatin was 53±2.59 years and 43.714±3.25 years respectively. 68% of the patients were using atorvastatin for secondary prevention and 32% for primary prevention. A total of 71.42% of the patients were prescribed with rosuvastatin for primary prevention and the remaining 28.57% for secondary prevention. (Table12).

In all the patients using atorvastatin, 68% of patient's target LDL level was <100mg/dl, 12% and 20% patient's target LDL-C level were <130mg/dl and <160mg/dl respectively. Similarly in case of patients who were on treatment with rosuvastatin the LDL goal was <100mg/dl for 28.57% of patients and < 130mg/dl and <160mg/dl for 42.85% and 28.57% respectively. (Table 13).

The outcomes of the therapy have been illustrated in Table 14. Out of the total 25 patients prescribed with Atorvastatin, 24 patients attained their target LDL-C level at first review. 7 patients were using rosuvastatin and 6 patients were able to achieve their target LDL level.

The mean baseline of the patients using atorvastatin 5mg, 10mg, 40mg and 80 mg were 77.33±16.20mg/dl, 145.25±21.96mg/dl, 101.77±12.24mg/dl, and 119.4±12.07mg/dl respectively. The mean baseline of the patients using Rosuvastatin 10mg was found to be 120.16±21.07md/dl. (Table15). The mean lipid reduction for atorvastatin 5mg, 10mg, 40mg and 80mg was found to be 3.3±9.9, 31.75±9.8, 33.25±9.714, 44.6±10.74 respectively and for Rosuvastatin 10mg was 28.33±12.95. (Table 15, Figure 10). The results revealed that there was a significant reduction in LDL-C level from the baseline at review in patients using Atorvastatin 10mg($p<0.02$), 40mg($p<0.01$) and 80mg(<0.02).There was also a considerable reduction in the LDL-C level eventhough the reduction was found to be insignificant in patients on treatment with Atorvastatin 5mg and Rosuvastatin 10mg.(Table 15).

Causality assessment of the reported adverse drug reactions are carried out by using Naranjo's causality assessment scale (Table 16). Muscle pain was only the ADR reported by the patients using Atorvastatin 40mg and 80mg and it was found as a possible reaction of the drug.

# *Tables and Graphs*

**TABLE 3: GENDER WISE DISTRIBUTION OF THE STUDY POPULATION.**

| GENDER | PERCENTAGE OF PATIENTS |
|---|---|
| Male | 93.75% |
| Female | 6.25% |

**FIGURE 1: GENDER WISE DISTRIBUTION OF THE STUDY POPULATION.**

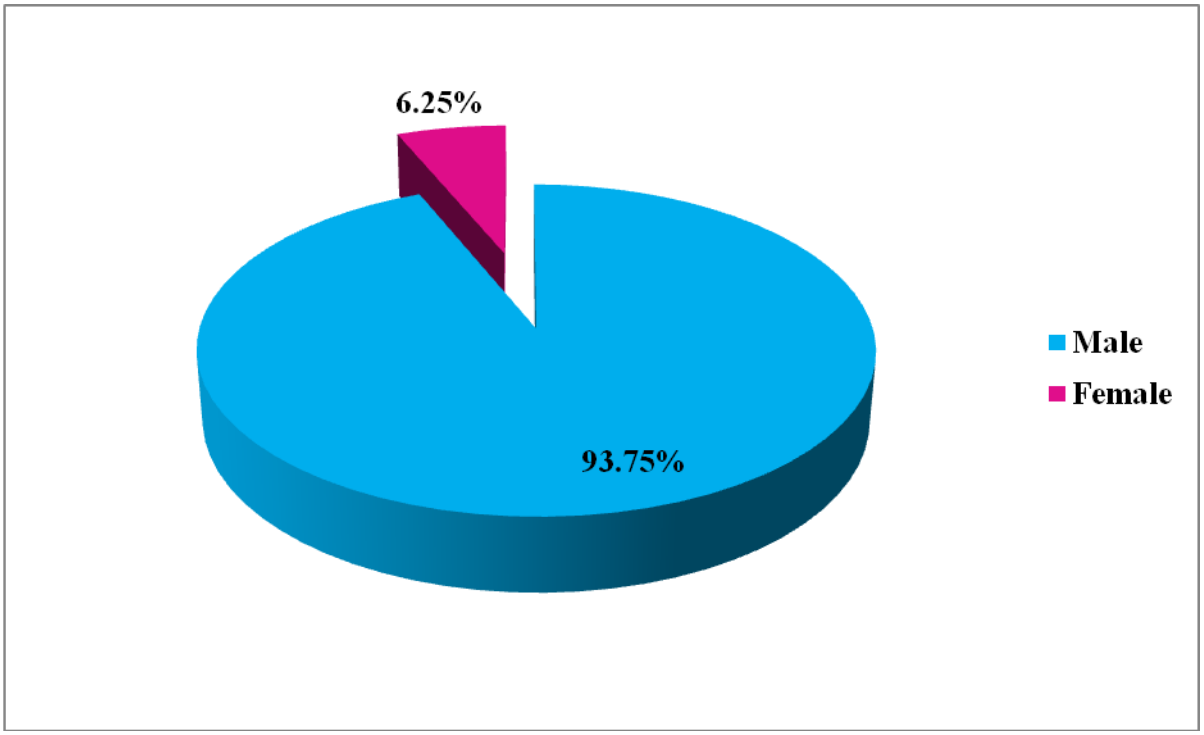


**TABLE 4: AGE WISE DISRIBUTION OF THE STUDY POPULATION.**

| AGE GROUP (YEARS) | PERCENTAGE OF PATIENTS |
|---|---|

| | |
|---|---|
| **21-30** | **6.25%** |
| **31-40** | **18.75%** |
| **41-50** | **21.87%** |
| **51-60** | **18.75%** |
| **61-70** | **34.37%** |

**FIGURE 2: AGE WISE DISRIBUTION OF THE STUDY POPULATION.**

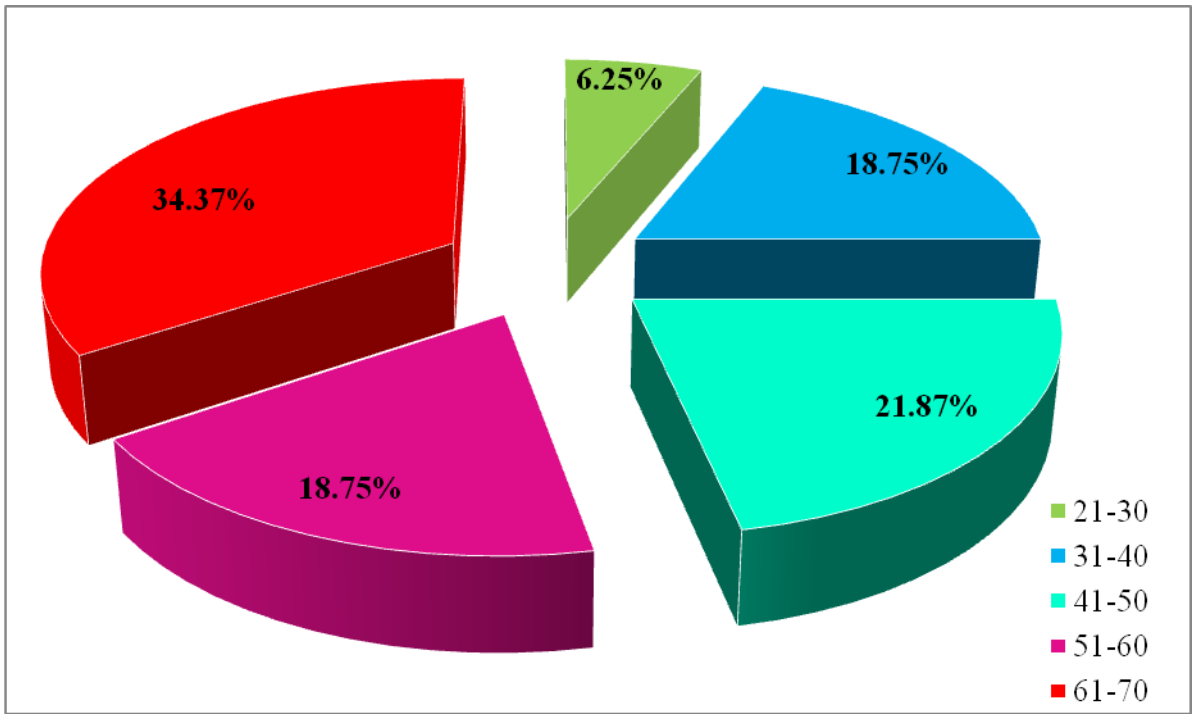


**TABLE: 5 CLASS OF STATIN PRESCRIBED.**

| PRESCRIBED CLASS OF STATIN | PERCENTAGE OF PATIENTS |
|---|---|
| ATORVASTATIN | 78.12% |
| ROSUVASTATIN | 21.88% |

**FIGURE: 3 CLASS OF STATIN PRESCRIBED.**

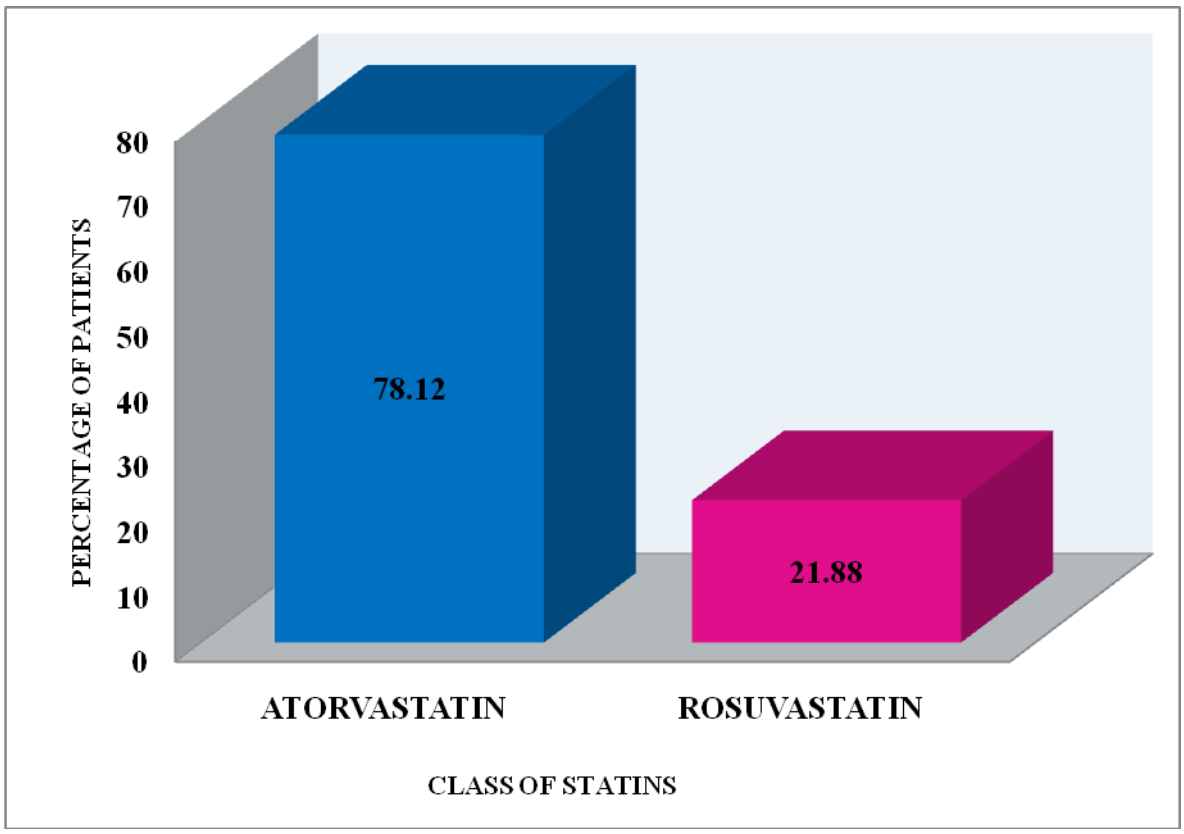


**TABLE 6: DOSEWISE DISTRIBUTION OF THE STUDY POPULATION.**

| PRESCRIBED DOSES OF STATIN | PERCENTAGE OF PATIENTS |
|---|---|
| Atorvastatin 5mg | 9.3% |
| Atorvastatin 10mg | 25% |
| Atorvastatin 20mg | 0% |
| Atorvastatin 40mg | 28.12% |
| Atorvastatin 80mg | 15.62% |
| Rosuvastatin 10mg | 18.75% |
| Rosuvastatin 20mg | 3.125% |

**FIGURE: 4 DOSE WISE DISTRIBUTION OF THE STUDY POPULATION.**

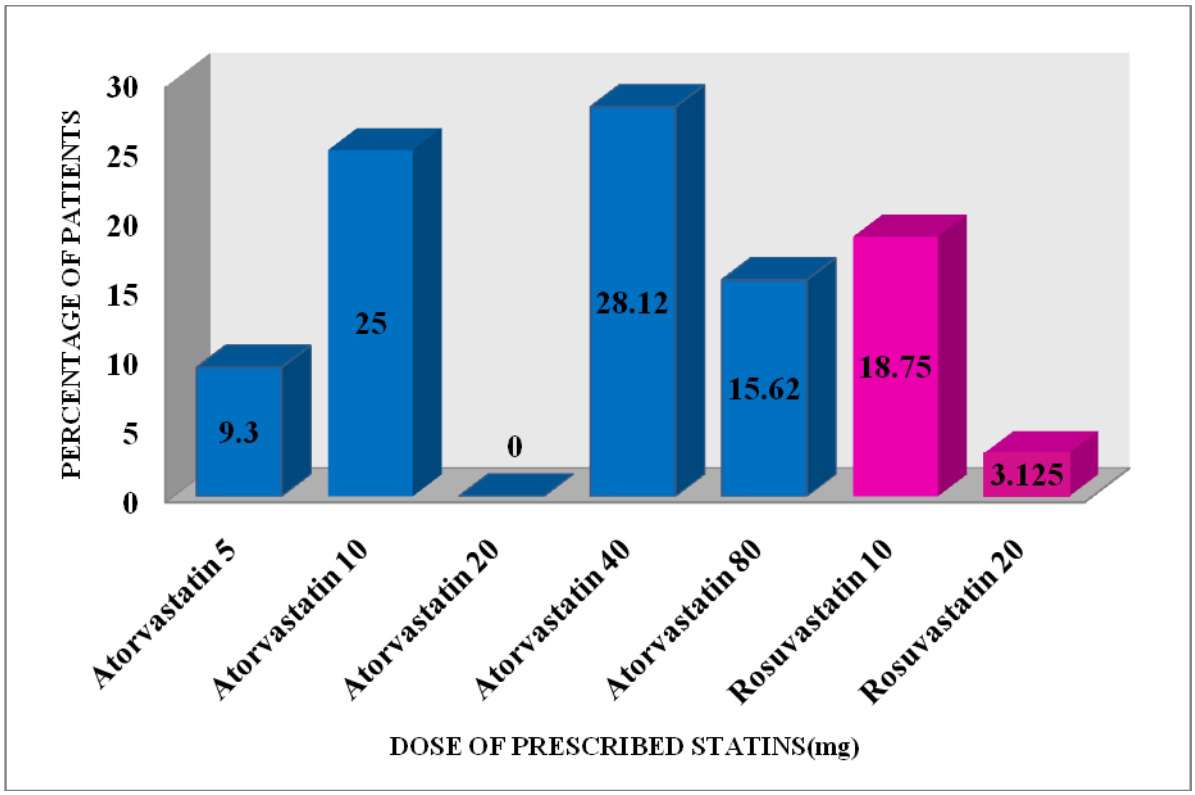

**TABLE 7: PERCENTAGE LIPID REDUCTION AT DIFFERENT DOSES OF PRESCRIBED STATINS.**

| PRESCRIBED DOSES OF STATIN | PERCENTAGE LIPID REDUCTION |
|---|---|
| ATORVASTATIN5mg | 21.29% |
| ATORVASTATIN10mg | 24.16% |
| ATORVASTATIN40mg | 17.83% |
| ATORVASTATIN80mg | 37.628% |
| ROSUVASTATIN10mg | 32.574% |

**FIGURE 5: PERCENTAGE LIPID REDUCTION AT DIFFERENT DOSES OF PRESCRIBED STATINS.**

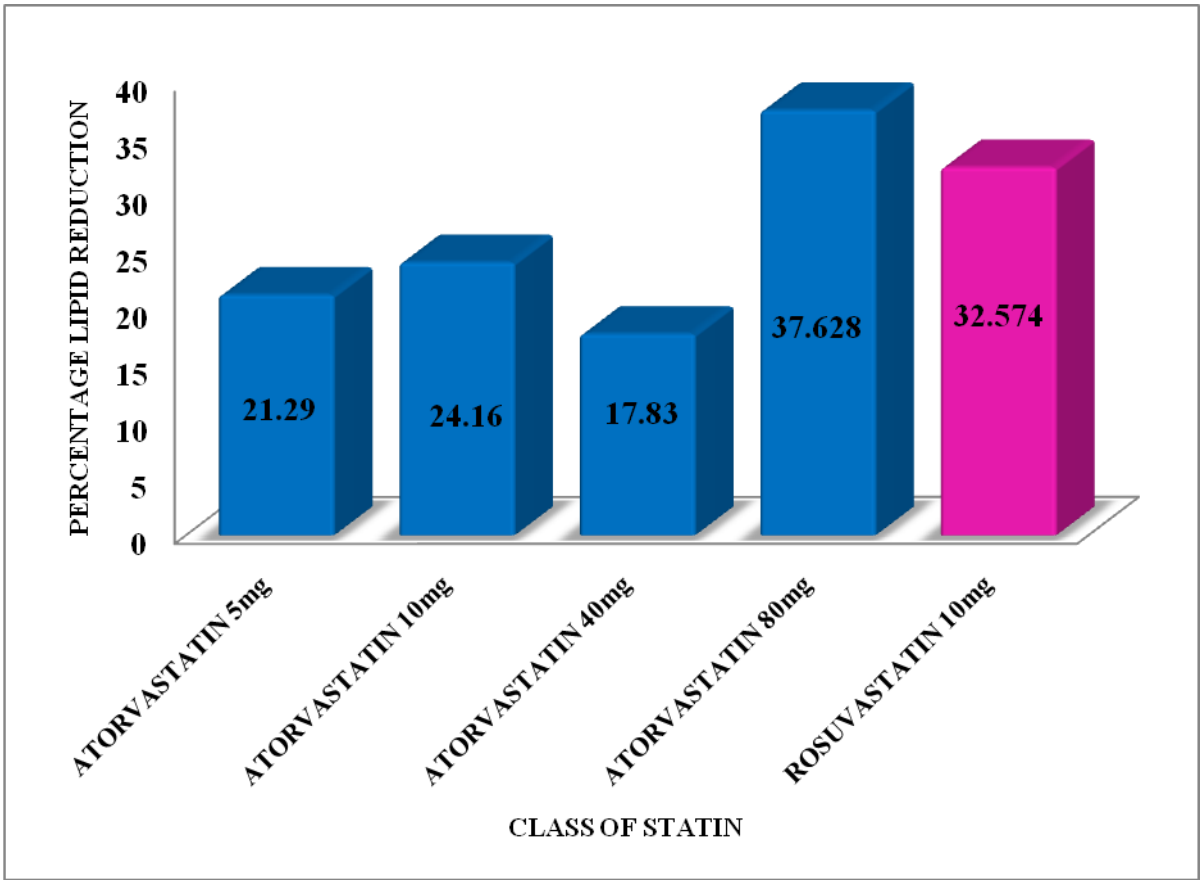

**TABLE 8: ASSESSMENT OF STATIN USE FOR THE PREVENTION OF CARDIOVASCULAR DISEASE.**

| TYPE OF PREVENTION | PERCENTAGE OF PATIENTS |
|---|---|
| PRIMARY | 40.62% |
| SECONDARY | 59.37% |

**FIGURE 6: ASSESSMENT OF STATIN USE FOR THE PREVENTION OF CARDIOVASCULAR DISEASE.**

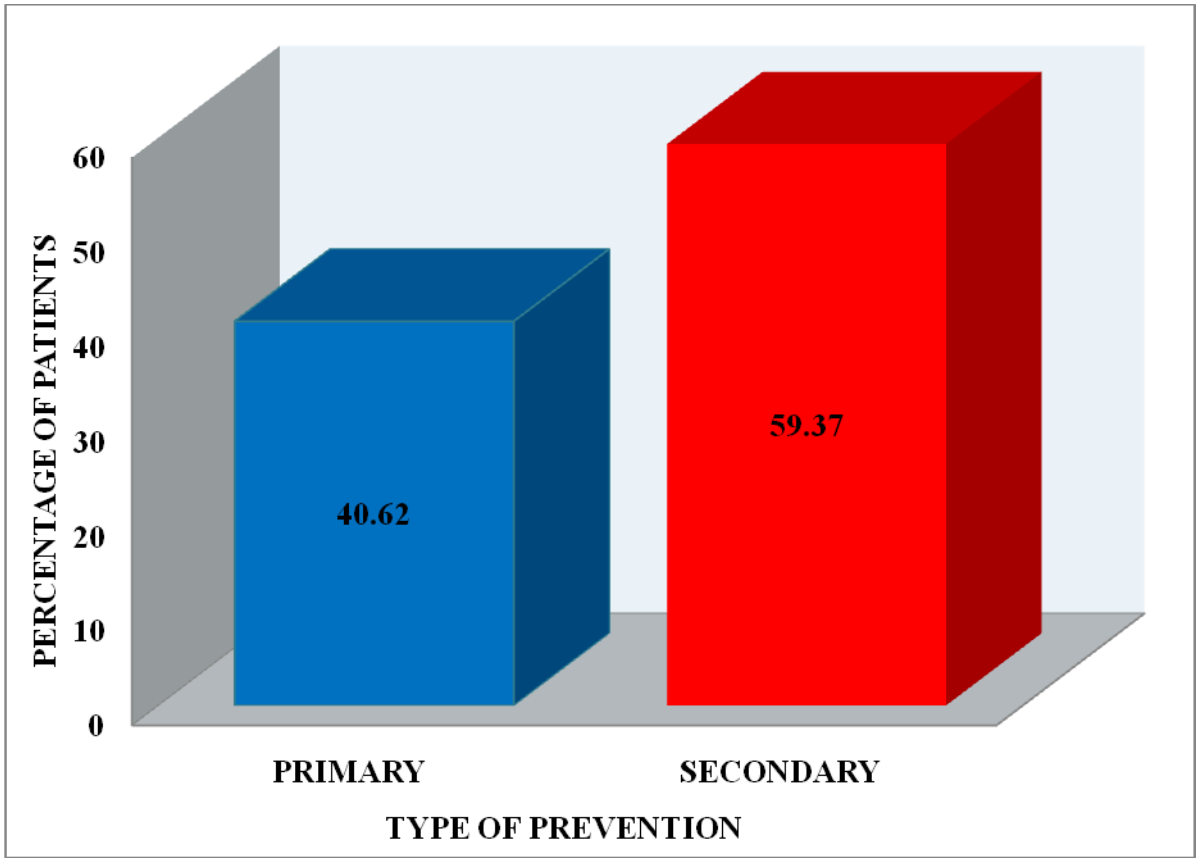

**TABLE 9: ASSESSMENT OF PATIENT ADHERANCE TO PRESCRIBED STATIN.**

| PATIENT ADHERANCE | PERCENTAGE OF PATIENTS |
|---|---|
| HIGH ADHERANCE | 67.74% |
| MEDIUM ADHERANCE | 22.58% |
| LOW ADHERANCE | 9.67% |

**FIGURE 7: ASSESSMENT OF PATIENT ADHERANCE TO PRESCRIBED STATIN.**

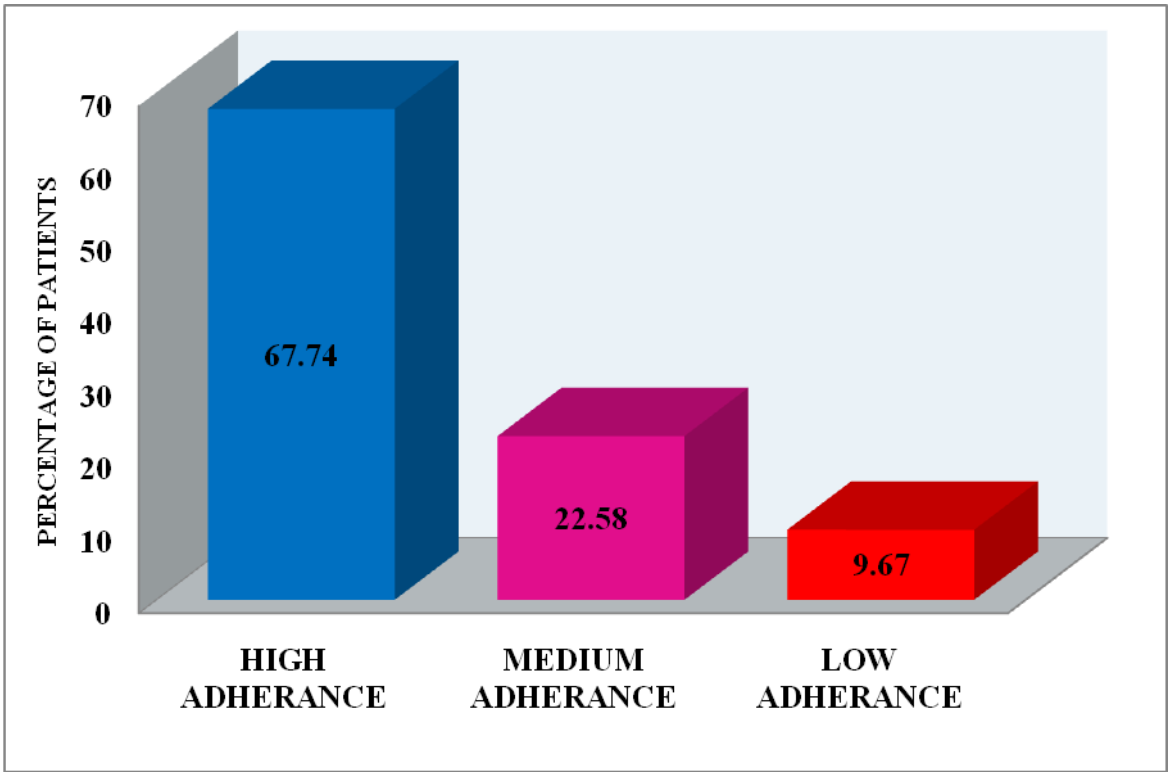

**TABLE 10: PERCENTAGE OF PATIENTS REPORTED ADVERSE DRUG REACTIONS.**

| ASSESSMENT OF ADR | PERCENTAGE OF PATIENTS |
|---|---|
| PATIENTS WITH MUSCLE PAIN | 25.8% |
| WITHOUT PAIN | 74.2% |

**FIGURE 8: PERCENTAGE OF PATIENTS REPORTED ADVERSE DRUG REACTIONS.**

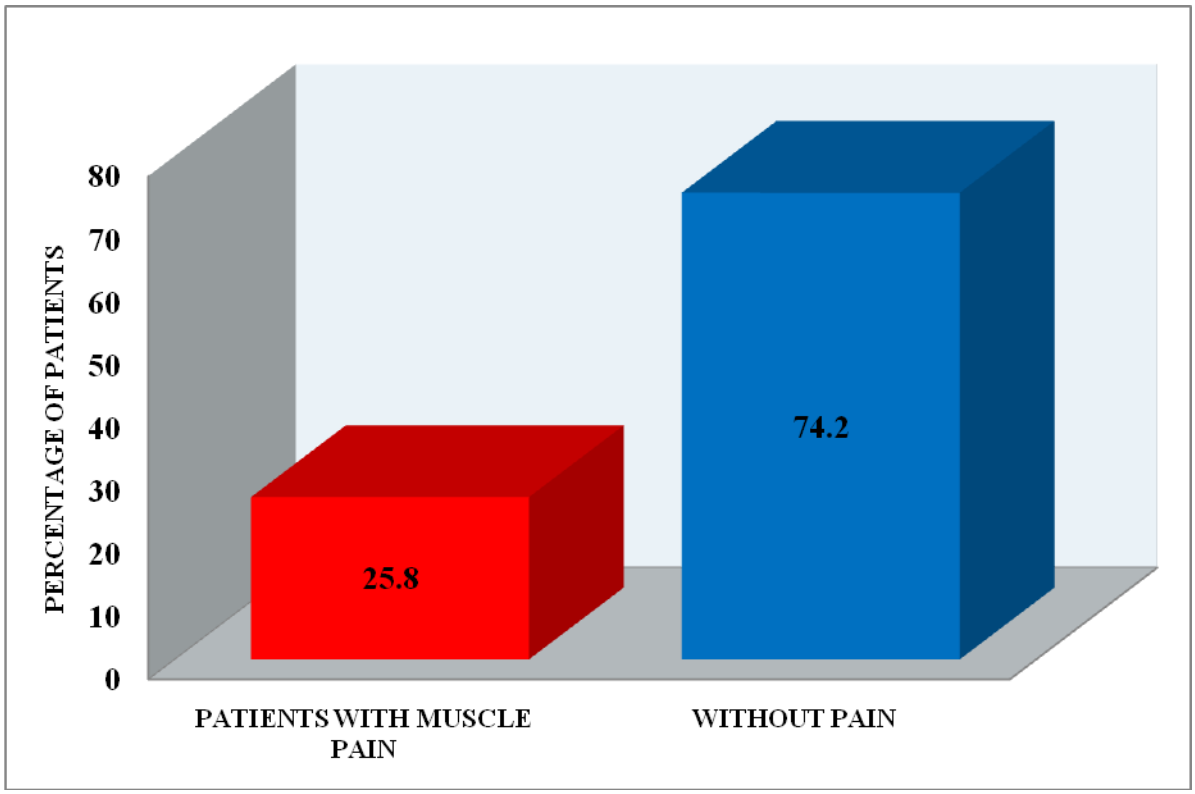

**TABLE 11: PREVALENCE OF ADR IN DIFFERENT AGE GROUPS OF THE STUDY POPULATION.**

| AGE GROUP (YEARS) | PERCENTAGE OF PATIENTS |
|---|---|
| 21-30 | 0% |
| 31-40 | 12.5% |
| 41-50 | 0% |
| 51-60 | 0% |
| 61-70 | 87.5% |

**FIGURE 9: PREVALENCE OF ADR IN DIFFERENT AGE GROUPS OF THE STUDY POPULATION.**

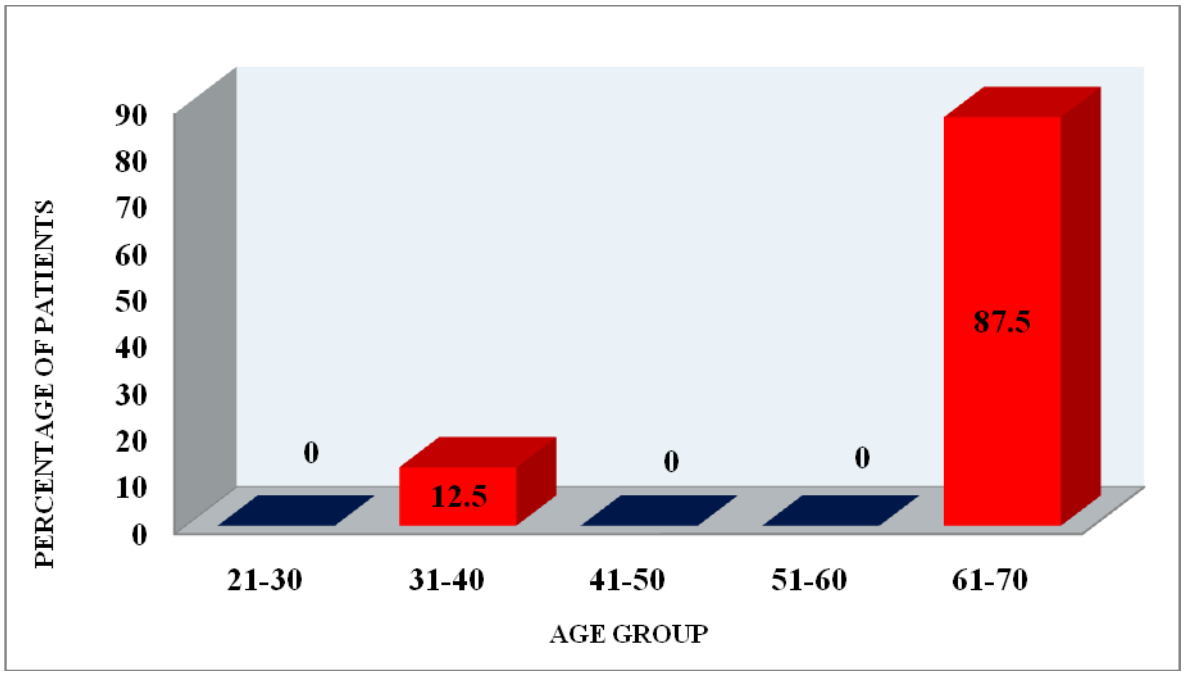

**TABLE 12: DEMOGRAPHIC CHARACTERISTICS OF THE PATIENTS USING STATINS.**

| DEMOGRAPHIC CHARACTERISTICS | ATORVASTATIN n(%) | ROSUVASTATIN n(%) |
|---|---|---|
| Gender | | |
| Male | 23(71.8) | 7(21.87) |
| Female | 2(6.25) | 0 |
| Age(mean ±standard Error, year) | 53±2.59 | 43.714±3.25 |
| Indication for cardiovascular prevention | | |
| Primary | 8(32) | 5(71.42) |
| Secondary | 17(68) | 2(28.57) |

**TABLE 13: THE TARGET OF THE THERAPY WITH THE PRESCRIBED DRUGS.**

| BASELINE LDL-C (mg/dl) | ATORVASTATIN | ROSUVASTATIN |
|---|---|---|
| Primary prevention | n(%) | n(%) |
| Goal LDL-C<160 | 5(20) | 2(28.57) |
| <130 | 3(12) | 3(42.85) |
| Secondary | | |
| Goal LDL-C<100 | 17(68) | 2(28.57) |

**TABLE 14: OUTCOMES OF THE THERAPY.**

| LDL GOAL(mg/dL) | TOTAL NUMBER | TARGET ACHIEVED | TARGET NOT ACHIEVED |
|---|---|---|---|
| <100 | | | |
| Atorvastatin | 17 | 16 | 1 |
| Rosuvastatin | 2 | 2 | 0 |
| <130 | | | |
| Atorvastatin | 3 | 3 | 0 |
| Rosuvastatin | 3 | 2 | 1 |
| <160 | | | |
| Atorvastatin | 5 | 5 | 0 |
| Rosuvastatin | 2 | 2 | 0 |

*(LDL GOALS ARE DECIDED BY NCEP- ATP III GUIDELINES)*

**TABLE 15: LDL-C REDUCTION AT FIRST REVIEW (mg/dl).**

| DRUG | BASELINE LDL-C LEVEL(MEAN ± SE) | LDL-C AT REVIEW(MEAN ±SE) | LDL-C REDUCTION(MEAN ± SE) | P VALUE |
|---|---|---|---|---|
| Atorvastatin 5mg | 77.33±16.20 | 74±6.65 | 3.3±9.9 | <0.7 |
| Atorvastatin 10mg | 145.25±21.96 | 113.5±16.18 | 31.75±9.8 | <0.02* |
| Atorvastatin 40mg | 101.77±12.24 | 66.11±7.49 | 33.25±9.714 | <0.01** |
| Atorvastatin 80mg | 119.4±12.07 | 74.8±11.33 | 44.6±10.74 | <0.02* |
| Rosuvastatin 10mg | 120.16±21.07 | 74.8±11.44 | 28.33±12.95 | <0.1 |

**FIGURE 10: LDL-C REDUCTION AT FIRST REVIEW.**

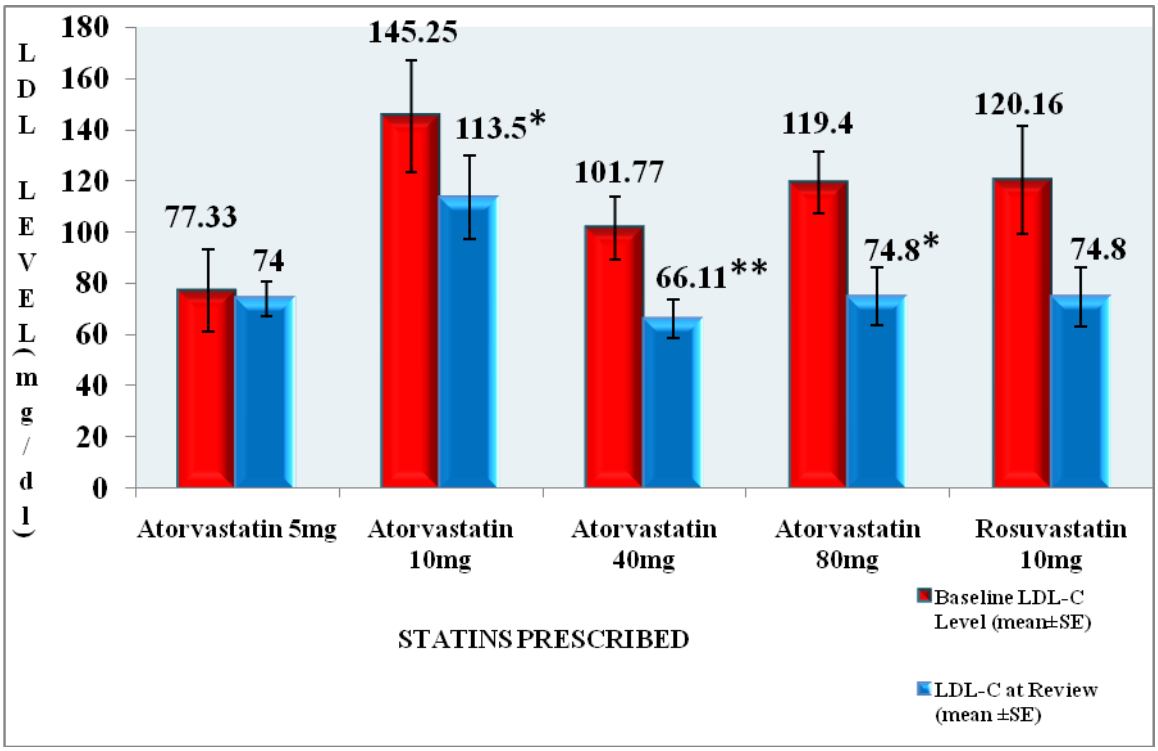


**TABLE 16: CAUSALITY ASSESSMENTS.**

| DRUG | TOTAL NUMBER OF PATIENTS | NUMBER OF PATIENTS REPORTED ADR | REPORTED ADR | CAUSALITY |
|---|---|---|---|---|
| **ATORVASTATIN** | | | | |
| 5mg | 3 | Nil | Nil | Nil |
| 10mg | 8 | Nil | Nil | Nil |
| 20mg | 0 | Nil | Nil | Nil |
| 40mg | 9 | 3 | Muscle pain | Possible |
| 80mg | 5 | 5 | Muscle pain | Possible |
| **ROSUVASTATIN** | | | | |
| 5mg | 0 | Nil | Nil | Nil |
| 10mg | 6 | Nil | Nil | Nil |
| 20mg | 1 | Nil | Nil | Nil |

# *Discussion*

# DISCUSSION

In a study conducted in Warangal district of Andhra Pradesh with 1496 adults, dyslipidemia was found in 52.7% males and 42.9% were females. The incidence dyslipidemia was predominant in all age groups, but in middle age group (40– 59 years) this increase was found to be highly significant. (**Estari et al., 2009**). The patients prescribed with statins for dyslipidemia were at younger age group when compared to the non users of statins and males are more in this category (**Molnaret et al., 2011**). In our study population also the prevalence of dyslipidemia was higher in males than in females, 93.75% of the patients were males and the remaining 6.25% of the patients were females.

The frequency of cardiovascular events increases sharply with the increase in age. The incidence of cardiovascular disease and associated risk factors are considerably higher in older individuals. Cardiovascular disease is the most important reason for death in older patients, out of this, over 80% of deaths are reported due to coronary heart disease (CHD) or stroke occur in individuals of 65 years of age or older. So the prevention and recurrence of cardiovascular events in older individuals remains a major concern. (**Wenger et al., 2010**). However in our study we found that maximum number of patients was diagnosed with dyslipidemia at an age group of 61-70years.

In a study conducted in Thailand almost 90% of the subjects included in the study were prescribed with simvastatin. Atorvastatin and pravastatin were used by only 8% and 2% patients respectively. It was found that about 58% of the patients were on statin therapy for primary prevention (**Chaiyakunapruk et al., 2011**)**.** In our study population 78.12% of the patients were prescribed with atorvastatin and 21.88% of the patients were using rosuvastatin. Among all the classes of statin atorvastatin 40mg was prescribed in most of the patients

(28.12%). In our study we assessed the statin use in terms of type of prevention and found that 59.37% of patients were prescribed for secondary prevention and the remaining 40.62% of patients were on treatment with statins for primary prevention of cardiovascular diseases.

The mean lipid reduction by atorvastatin at doses of 5mg, 10mg, 20mg, 40mg and 80mg was 45%, 37%, 43%, 50% and 53% respectively. (**Chaiyakunapruk et al., 2011**)**.** In our study population atorvastatin 80mg (37.62%) was found to produce maximum lipid reduction among all the other classes of statins in the study population and the least by Atorvastatin 40mg (17.83%). Atorvastatin showed a mean lipid reduction of 21.29%,24.16% at doses like 5mg and 10mg respectively. Rosuvastatin 10mg showed 32.574% LDL-C reduction at review.

In a study conducted in a health maintenance organization setting it was found that persons aged below 50 years were at high risk of poor adherence to statin therapy and the assessment proposed that the relationship between age and gender may be reasonably steady after three years of therapy with statins. (**Caspard et al., 2005**). Morisky's 8 questionnaire was used in our study to check the patient's adherence to statin therapy and it was found that 67.4 % of patients were highly adherent to their treatment plan. 22.58% of patients showed medium adherence and 9.67% of patients showed low adherence to their treatment plans. The results are encouraging that patients are compliant with the therapy and hence cardiovascular protection can be expected.

There was no muscle pain and associated adverse drug reactions were not detected on treatment with statins. (**Taylor et al., 2011)**. Recent investigations reveal that age, race, work outs, and perioperative conditions may contribute to statin induced muscle toxicity. (**Antons et al., 2006**).The finding of our study was also the same .Statins are well tolerated in most of the patients. Muscle pain was the only Adverse Drug Reaction found in the study

population.74.2% of the patients was free from muscle pain and 25.8% patients complained about muscle pain. The adverse drug reactions and patient's age were related in the study population. 87.5% of the patients who developed muscle pain were at an age group of 61-70 years and only 12.5% of patients were at an age group of 21-30 years. The prevalence of ADR was found to be more in geriatric population.

The mean age of the patients using atorvastatin was 59.8±0.8, and 70.6% of the patients were using atorvastatin for primary prevention and 29.4% of the patients were using it for secondary prevention in a study carried out in Thailand (**Chaiyakunapruk et al., 2011**). Similiarly, in our study the mean age of the patients using atorvastatin was 53±2.59 years. However we found that 68% of the patients were using atorvastatin for secondary prevention and 32% for primary prevention.

Researchers have noted that in a population of 6814 patients, 30% of the patients were diagnosed with dyslipidemia, 54.0% patients reported the use of statin therapy and the target was achieved in 75.2% of patients. **(Goff et al., 2006)**. In our study population, Out of the total 25 patients prescribed with atorvastatin, 24 (96%) patients attained their target LDL-C level at first review. 7 patients were using rosuvastatin and 6 patients were able to achieve their target LDL-C level.

# *Conclusion*

# CONCLUSION

The aim of the study was to assess the statin use in an Indian clinical setting in terms of class, dose, and type of prevention and monitoring of Adverse Drug Reactions. In the study population atorvastatin was prescribed in 78.12% of patients and rosuvastatin was prescribed in 28.87% of the patients only. Most of the patients are prescribed with atorvastatin 40mg (28.12%) and the least number of patients were prescribed with rosuvastatin 20mg (3.12%).

The lipid reduction properties of statins were assessed by measuring the LDL-C level of the patients at baseline and at review. The study revealed that at review, atorvastatin showed a significant reduction in LDL-C level from the baseline at prescribed doses 10mg, 40mg, and 80mg. There was a substantial reduction in the LDL-C level from the baseline in the patients prescribed with atorvastatin 5mg and rosuvastatin 10mg at review, eventhough the reduction was found to be non significant.

The study was also aimed to check the efficacy of statin to achieve the target LDL-C level of the patients and it was found that 93.75% of the patients achieved their target LDL-C level on treatment with statins.

The Adverse Drug Reactions were monitored and related to different characteristics of the study population. The main ADR found in the study population was muscle pain and was predominant in the age group of 61-70 years. The baseline LDL-C of the patients prescribed with atorvastatin 10mg (145.25±21.96) was found to be higher than that of the patients with atorvastatin 40mg (101.77±12.24).

The adherence of the patients to prescribed statin was checked by using Morisky's-8 questionnaire and it was found that 67.4 % of patients were highly adherent to their treatment

plan. 22.58% of patients showed medium adherence and 9.67% of patients showed low adherence to their treatment plans.

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# *Annexures*

# KMCH ETHICS COMMITTEE

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**Ref: EC/AP/165/10/2011**
**24.10.2011**

APPROVED

To

Dr.Suchandra Sen, M.Pharm, PhD

Department of Pharmacy Practice,

KMCH College of Pharmacy,

Coimbatore-641048

Tamilnadu, India.

Dear Dr. Suchandra Sen,

The proposal entitled **"Utilization pattern of statins in Indian Population"** submitted by Mr.Nikhil Raj was reviewed by the Ethics Committee in its meeting held on 22.10.2011 and permission is granted to you to carryout the study at Kovai Medical Center and Hospital Ltd, Coimbatore, India.

Thanking you,

Yours faithfully,

24/10/'11

**Dr. P. R. Muthuswamy**
**Chairman, Ethics Committee**

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10.03.2012

## CERTIFICATE

This is to certify that the research work entitled **" UTILIZATION PATTERN OF STATINS IN AN INDIAN POPULATION"** carried out by **Mr. NIKHIL RAJ. P.V.,** submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the degree of Master of Pharmacy in Pharmacy Practice is a bonafide work carried out by the candidate under my supervision at the Department of Cardiology, Kovai Medical Center and Hospital, Coimbatore, during the academic year of 2011 to 2012.

**DR.SURESHKUMAR.R., MD DM.,**
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## MORISKY'S ADHERANCE SCALE

| QUESTION | PATIENT ANSWER [Yes or No] | SCORE |
|---|---|---|
| 1. Do you sometimes forget to take you medicine? | | Y=1, N=0 |
| 2. People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine? | | Y=1, N=0 |
| 3. Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it? | | Y=1, N=0 |
| 4. When you travel or leave home, do you sometimes forget to bring along your medicine? | | Y=1, N=0 |
| 5. Did you take all your medicine yesterday? | | Y=0, N=1 |
| 6. When you feel like your symptoms are under control, do you sometimes stop taking your medicine? | | Y=1, N=0 |
| 7. Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan? | | Y=1, N=0 |
| 8. How often do you have difficulty remembering to take all your medicine?<br>____ A. Never/rarely<br>____ B. Once in a while<br>____ C. Sometimes<br>____ D. Usually<br>____ E. All the time | | A = 0,<br>B-E = 1 |
| | Total Score | |

NARANJO's ALGORITHM

| question | Yes | No | Don't know |
|---|---|---|---|
| Are there previous conclusion reports on this reaction? | +1 | 0 | 0 |
| Did the adverse event appear after the suspect drug was administered? | +2 | -1 | 0 |
| Did the AR improve when the drug was discontinued or a specific antagonist was administered? | +1 | 0 | 0 |
| Did the AR reappear when drug was readministered? | +2 | -1 | 0 |
| Are there alternate causes [other than the drug] that could solely have caused the reaction? | -1 | +2 | 0 |
| Did the reaction reappear when a placebo was given? | -1 | +1 | 0 |
| Was the drug detected in the blood [or other fluids] in a concentration known to be toxic? | +1 | 0 | 0 |
| Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? | +1 | 0 | 0 |
| Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1 | 0 | 0 |
| Was the adverse event confirmed by objective evidence? | +1 | 0 | 0 |